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IS OBESITY A DISEASE?

Abstract: Obesity is a complex entity that can have many causes, such as endocrine (like thyroid dysfunction or hyperfunctioning of the suprarenall gland-Cushing's syndrome) but often obesity is from a combination of inactivity and overeating. On the other side, there are genetic factors that produce a tendency to overweight even with the consumption of what would be for most people an appropriate number of calories. Whether the causes are hormonal, genetic or reside in the brain (its reward system or the circuitry that underlies habit, perception of portion size, the choice of food...) is often difficult to sort out. Proponents contend that obesity is a disease because it meets the definition of disease. Obesity decreases life expectancy and impairs the normal body functions, also it can be caused by genetic factors. Opponents contend that obesity is not a disease because it is a preventable risk factor for other diseases. Obesity is the result of eating too much as well as it is caused by exercising too little. Formaly disease or condition obesity is associated with a variety of diseases such as type 2 diabetes, atherosclerosis, cardiovascular diseases and certain cancers, and may also be responsible for high rates of morbidity and mortality. Understanding the pathophysiology of obesity has grown significantly over the last few decades. Pathogenetic mechanisms in obesity and in the development of comorbidities that accompany obesity exhibit many of the characteristics of inflammatory processes. A key role in the pathogenesis of obesity could play the immune system. Despite identifying many critical players in these processes and finding new therapeutic modalities in the fight against obesity, treatment of obesity is still a great challenge and mostly with not-so-successful outcomes.

Key words: obesity, inflammation, comorbidity, white adipose tissue, brown adipose tissue

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Introduction

Obesity is associated with a variety of medical conditions such as type 2 diabetes, atherosclerosis, cardiovascular diseases and some cancers and is therefore responsible for high morbidity and mortality rates in these population. According to the latest statistics of the world health organization, the worldwide prevalence of obesity, has nearly doubled since 1980 and at least 2.8 million people die each year as a result of obesity. This number is expected to further increase over the next decade (1). Obesity is a complex entity that can have many causes, such as endocrine (like thyroid dysfunction or hyperfunctioning of the suprarenall gland-Cushing's syndrome) but often obesity is from a combination of inactivity and overeating. On the other side, there are genetic factors that produce a tendency to overweight even with the consumption of what would be for most people an appropriate number of calories. Whether the causes are hormonal, genetic or reside in the brain (its reward system or the circuitry that underlies habit, perception of portion size, the choice of food...) is often difficult to sort out. Proponents contend that obesity is a disease because it meets the definition of disease. Obesity decreases life expectancy and impairs the normal body functions, also it can be caused by genetic factors. Opponents contend that obesity is not a disease because it is a preventable risk factor for other diseases. Obesity is the result of eating too much as well as it is caused by exercising too little.

Pathogenetic mechanisms in obesity and in the development of comorbidities that accompany obesity exhibit many of the characteristics of inflammatory processes (2). A key role in the pathogenesis of obesity could play the immune system. Despite identifying many critical players in these processes and finding new therapeutic modalities in the fight against obesity, treatment of obesity is still a great challenge and mostly with not-so-successful outcomes. Hence the talk and explore similarities and links between obesity and atherosclerosis exist in order to treat and prevent both conditions. Interestingly, recent studies have shown that activation of beige or brown adipocytes, and, consequently, increase in energy consumption can reduce the mass of fat tissue in the body and potentially reduce the inflammation of body fat (3). There is evidence that the function of brown and beige fat tissue is regulated by immune processes (4). The current strategy is to increase the energy consumption of brown adipose tissue (BAT) in order to reduce excessive energy depots in obesity. Interventions in immune pathways could precede the development of new strategies to increase the activity of brown and beige adipose tissue as a therapeutic target for obesity.

The role of low grade inflammation in pathogensis of obesity and associated comorbidity

The first proof that inflammation is important in the pathogenesis of obesity and the resulting metabolic dysfunction was provided by Hotamasligil et al (5). The pro-inflammatory cytokine tumor necrosis factor-α (TNF) was found to be present in WAT and correlated with insulin resistance in humans and mice (5). It became evident that the infiltration of proinflammatory macrophages in WAT plays a central role in the inflammatory response as main source of TNF (6). In WAT of lean mice, 10-15% of the cells are macrophages, whereas obese WAT contains 45-60% macrophages (6). Resident macrophages in lean WAT have a predominant anti-inflammatory phenotype, whereas in obesity, inflammatory monocytes are recruited to WAT, where they differentiate, acquire a proinflammatory or M1 phenotype and form the majority of macrophages (7). Antiinflammatory or M2 macrophages depend on the cytokines IL-4 and IL-13 and require STAT6 to maintain their alternative activation condition (8). Other myeloid cells that play a role in WAT include neutrophils and eosinophils. Neutrophils are very short-lived cells that are already present in WAT within 3 days of HFD (9). In contrast, the number of eosinophils is inversely correlated with adiposity, and exhaustion of eosinophils in mice results in increased body weight, glucose intolerance and insulin resistance (10). Both type 2 innate lymphoid cells (ILC2s) and eosinophils have only recently been shown to be an important cell population in WAT and are a predominant source of IL-4 and IL-13, the cytokines required for the induction of M2 macrophage polarization (10). Lymphoid cell infiltration in WAT T cells are also a component of the repertoire of immune cells found in WAT. Ten percent of the stromal vascular fraction of lean WAT consists of T cells. A large part of these are CD4+ T-helper cells, of which approximately 50% are regulatory T cells (Tregs). In humans, the number of T cells in WAT correlates with BMI (11). In mice, the amount of T cells in WAT increases within 2 weeks of HFD. There are only a few CD8+ cytotoxic T cells and CD4+ effector T cells in lean WAT, but both populations increase drastically in an obese state, whereas CD4+ Tregs decrease (121). Similarly, as the ratio between M1 and M2 macrophages increases in obese WAT, the Th1 and Th2 T cell ratio does as well. This results in a decrease in Th2 derived cytokines such as IL-4 and IL-13, thereby reducing M2 macrophage polarization. An increase in Th1 T cells and cytotoxic T cells results in excessive secretion of TNF and IFNγ, which polarizes macrophages to a pro-inflammatory state, resulting in increased inflammation in obese WAT (10,12). The chronic low-grade inflammation in obese WAT also includes the recruitment of B cells, natural killer (NK) cells and mast cells (13). NK cells are activated by recognition of lipid antigens and mast cells contain granules that can release

a variety of mediators, including histamine, serotonin and cytokines, which also promote recruitment of inflammatory cell types (13).

The role of brown and beige adipose tissue

In contrast to the established role of the different immune cells in WAT, the contribution of the immune system to the development, function and activity of BAT is still largely unknown. However, we do know that obese individuals have a decreased amount of active BAT, based on FDG uptake, which is related to their low-grade inflammatory state. Moreover, an inactive brown adipocyte accumulates lipids, similar to a white adipocyte and ablation of noradrenergic input by selective sympathetic denervation of BAT indeed results in a 'whitened' appearance of brown adipocytes with large intracellular vacuoles. Since the recruitment of macrophages into WAT is correlated with lipolysis of stored triglycerides (14), it is likely that release of fatty acids also induces recruitment of immune cells in BAT. However, whether this is indeed the case is still unknown. In diet-induced obesity (DIO), thermoneutral housing leads to an additive increase in inflammation in white adipose tissue and in the vasculature compared to normal housing conditions. Although not causing increased insulin resistance, the increase in vascular inflammation does cause enhanced progression of atherosclerosis (14), indicating that BAT protects against obesity-induced atherosclerosis. In another study, a similar phenomenon was observed. Immune compromised nude mice experience cold stress when housed at 23°C which modulates energy and body weight homeostasis and are therefore protected from DIO. However, at thermoneutrality (33°C), they do develop DIO with increased adiposity, hepatic triglyceride accumulation, increased inflammatory markers and glucose intolerance (15), showing that BAT activity protects against metabolic disarray and adipose tissue inflammation. Besides environmental temperature, other incentives such as the biological clock (16), hormones (17) and food intake not only modulate energy expenditure via the hypothalamus but also affect inflammation. For instance, time-restricted feeding of HFD for 8 hours per day increases BAT activity and reduces adipocyte hypertrophy and inflammation in WAT compared to ad libitum HFD-fed mice (18). Gut hormones such as GLP-1 mediate effects on food intake, energy expenditure and inflammation. GLP-1 receptor signaling activates BAT and promotes beiging of WAT (19,20) while GLP-1 also reduces macrophage infiltration and inflammatory signalling in white adipocytes and macrophages (21,22). Other hormonal changes such as menopause also affect energy metabolism. Estradiol inhibits AMPK in the hypothalamus, which activates thermogenesis in BAT (18). Indeed, ovariectomised mice with reduced estradiol levels gain more weight than sham operated mice and have reduced energy expenditure and increased WAT inflammation (23).

Clinical implications

Excessive energy intake results in increased storage of lipids in both white and brown adipocytes, which challenges the function of these cells. Immune cells and signals in WAT (white adipose tissue) and BAT are indispensable for the homeostasis of the tissue and contribute to the efflux of lipids stored in white adipocytes and to high rates of oxidation in brown and beige adipocytes. Immune cells, including eosinophils and alternatively activated macrophages, have regulatory roles in metabolic homeostasis of both WAT and BAT. Research to identify immunological players is ongoing. If the mechanism is unravelled in detail, immune regulation is an intriguing therapeutic target in increasing energy expenditure to reduce weight gain. Notably, the numbers of immune cells in lean as well as obese BAT are muchlower than in WAT, indicating that BAT is relatively more resistant to diet induced inflammation, but increased tissue inflammation in BAT does occur upon a positive energy balance. The challenge is to identify the metabolic crosstalk between immune cells and brown, beige and white adipocytes and the order of events that occur during obesity development. Important questions to further address include: What are the immune regulatory effector molecules that are secreted by brown adipocytes (or a pre-beige adipocyte or a white-wanting-to-become beige adipocyte) to attract or regulate immune cells? How is BAT activity regulated in obesity? What is the role of the sympathetic nerve system? And how does BAT activity change during aging? The presence of BAT in humans and the potential activation of resident BAT or induction of beige adipocytes in WAT is an interesting target to treat or even prevent obesity-related disorders. Cold is still by far the strongest sympathetic signal to activate BAT, but the quest for identifying biochemical and immunological pathways that are responsible for BAT activation, and thereby can bypass prolonged cold exposure, is ongoing. The recent finding on the role for immune cells in brown and beige adipocyte development and physiology harbours a great potential to increase BAT activity and beneficially alter energy metabolism by interfering in immune responses.

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